1]benzothiazepine-6,6-dioxide, on neurological scores in the Experimental Allergic Encephalomyelitis (EAE) of female DA rats at doses of 1, 3 and 10 mg/kg when administered orally (p.o.) as compared to vehicle and dexamethasone.

The following examples are being presented to further illustrate the invention. However, they should not be construed as limiting the invention in any manner.

EXAMPLE 1

Effects of Thiazolobenzoheterocyclic Compounds in SJL/J Mouse EAE, an Animal Model of Multiple Sclerosis.

The utility of the thiazobenzohetercyclic compounds of formula I for the treatment of various conditions associated with multiple sclerosis can be assessed by measuring their ability to inhibit effects of experimental allergic encephalomyelitis (EAE) in laboratory animals.

Experimental Autoimmune Encephalomyelitis (EAE) is a T-cell-mediated autoimmune disease of the nervous system that develops in susceptible animals following sensitization with either whole spinal cord homogenate or a myelin component. It is known that EAE reflects or mimics many of the pathophysiological steps in MS, including the role of certain adhesion molecules, the influence of T cells and antibodies reactive to components of the myelin sheath, the participation of metalloproteases in penetrating the blood-brain barrier, and the cytotoxic role of certain cytokines. One of the marketed MS therapies, glatiramer acetate (Copaxone®) was developed preclinically based on its success in treating various models of EAE.

EAE was induced in female SJL/J mice (8 wks old, from Jackson Laboratories) by immunization with the myelin Proteolipid Protein (PLP 139–151) from BACHEM, Bioscience. PLP139–151 was dissolved in H_2O:PBS (1:1) solution to a concentration of 7.5 mg/10 ml (for 75 ug PLP per mouse) and emulsified with an equal volume of CFA supplemented with 40 mg/10 ml heated-killed mycobacterium tuberculosis H37Ra (BD Bioscience). Mice were injected s.c. with 0.2 ml of peptide emulsion in the abdominal flank (0.1 ml on each side). On the same day and 72 hr later, mice were injected i.v. with 35 ng and 50 ng of Bordetella Pertussis toxin (List Biological Laboratories) in saline, respectively.

Mice were scored daily before treatment starting from day 7 post-immunization through the entire experiment by a well-known behavioral scale system: Score 0, normal; 0.5, partial limp tail; 1, complete limp tail; 2, impaired righting reflex; 2.5, significantly impaired righting reflex and notable weakness in hind limbs; 3, partial hind limb paralysis, and mice unable to walk normally; 3.5, one leg is completely paralyzed, and one leg is partially paralyzed; 4, complete hind limb paralysis; 4.5, Legs are completely paralyzed and Moribund; 5, death due to EAE. Compound A, one representative of thiazolobenzoheterocyclic compounds, was examined in the PLP/SJL mouse EAE model.

Study 1: There were five groups, i.e., vehicle (water), Compound A at doses of 5, 10 and 20 mg/kg and dexamethasone (DEX) at a dose of 3 mg/kg. Treatment was begun on day 7 after PLP immunization. Mice were dosed twice per day for 22 days. Results are as follows:

As seen in FIG. **1**, Compound A at doses of 10 and 20 mg/kg significantly reduced neurological deficits in the EAE mice

Study 2: There were five groups, i.e., vehicle (water), Compound A at doses of 10, 20 and 30/40 mg/kg and dexamethasone (DEX) at a dose of 3 mg/kg. Treatment was begun on day 7 after PLP immunization. Mice were dosed twice per day for 18 days. Results are as fellows:

At doses of 10 and 20 mg/kg, Compound A significant reduced neurological scores in SJL EAE mice. Further analyses shows that Compound A also reduced EAE incidence and delayed disease onset.

EXAMPLE 2

Effects of Thiazolobenzoheterocyclic Compounds in DA Rat EAE

EAE was induced in female DA (Dark Agouti) rats (8 wks old, from Harlan) by immunization with the 25% w/v rat spinal cord homogenate (r-SCH) in saline emulsified with an equal volume of CFA supplemented with 40 mg/10 ml heated-killed mycobacterium tuberculosis H37Ra (BD Bioscience). Rats were injected s.c. with 0.2 ml of emulsion in the base of tail.

Rats were scored daily before treatment starting from day 5 post-immunization through the entire experiment by a well-known behavioral scale system: Score 0, normal; 0.5, partial limp tail; 1, complete limp tail; 2, abnormal gait; 3, partial hind limb paralysis, and mice unable to walk normally; 3.5, one leg is completely paralyzed, and one leg is partially paralyzed; 4, complete hind limb paralysis; 4.5, Legs are completely paralyzed and Moribund; 5, death due to EAE. Compound A and Compound B (active metabolite of Compound A), two representatives of thiazolobenzoheterocyclic compounds, were examined in DA rat EAE procedure.

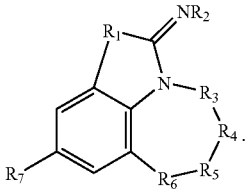
Compound A and Compound B were given one-day post-immunization, p.o. route, twice daily for 28 days. Results are as fellows:

At doses of 1, 3 and 10 mg/kg, both Compounds A and B significantly reduced EAE incidence, maximal and cumulative neurological scores.

What is claimed is:

1. A method of treating multiple sclerosis which comprises administering to a patient having multiple sclerosis a therapeutically effective amount of a compound of Formula I,

(I)



in which

R_1 is a sulphur or selenium atom,

R_2 is a hydrogen atom or an alkyl radical,

—R_3—R_4—R_5—R_6— is a chain of formula —CH_2—CH_2—CH_2—CH_2—, —CH_2—CH_2—CH_2—CO—, —CH_2—CH_2—CH_2—CH(R_8)—, —CH_2—CH_2—CH_2—Se—, —CH_2—CH_2—Se—CH_2—, —CH_2—CH_2—CH_2—S—, —CH_2—CH_2—CH_2—SO—, —CH_2—CH_2—CH_2—SO_2—, —CH_2—CH_2—CH_2—O—, —CH_2—CH_2—CH_2—N(R_9)—, —CH_2—CH_2—CO—CH_2—, —CH_2—CH_2—CH(R_8)—CH_2—, —CH_2—CH_2—S—CH_2—, —CH_2—CH_2—SO—CH_2—, —CH_2—CH_2—SO_2—CH_2—, —CH_2—C(alk)(alk')—S—CH_2—, —CH_2—C(alk)(alk')—SO—CH_2—, —CH_2—C(alk)(alk')—SO_2—CH_2—, —CH_2—CH(R_{10})—S—CH_2—, —CH_2—CH(R_{10})—SO—CH_2—, —CH_2—CH(R_{10})—SO_2—CH_2—, —CH_2—CH_2—O—CH_2—, —CH_2—CH_2—N(R_9)—CH_2— or —CH_2—CO—N(R_9)—CH_2—,